Blood 25-Hydroxy Vitamin D Levels and Incident Type 2 Diabetes

A meta-analysis of prospective studies

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OBJECTIVE—To quantitatively assess the strength and shape of the association between blood 25-hydroxy vitamin D [25(OH)D] levels and incident risk of type 2 diabetes.

RESEARCH DESIGN AND METHODS—A systematic search of the MEDLINE and Embase databases and a hand search of references from original reports were conducted up to 31 October 2012. Prospective observational studies that assessed the association between blood levels of 25(OH)D and risk of incident type 2 diabetes were included for meta-analysis. DerSimonian and Laird's random-effects model was used. A quadratic spline regression analysis was used to examine the shape of the association with a generalized least-squares trend test performed for the dose-response relation.

RESULTS—A total of 21 prospective studies involving 76,220 participants and 4,996 incident type 2 diabetes cases were included for meta-analysis. Comparing the highest to the lowest category of 25(OH)D levels, the summary relative risk for type 2 diabetes was 0.62 (95% CI 0.54–0.70). A spline regression model showed that higher 25(OH)D levels were monotonically associated with a lower diabetes risk. This inverse association did not differ by sex, duration of follow-up, study sample size, diabetes diagnostic criteria, or 25(OH)D assay method. A linear trend analysis showed that each 10 nmol/L increment in 25(OH)D levels was associated with a 4% lower risk of type 2 diabetes (95% CI 3–6; P for linear trend < 0.0001).

CONCLUSIONS—Our meta-analysis showed an inverse and significant association between circulating 25(OH)D levels and risk of type 2 diabetes across a broad range of blood 25(OH)D levels in diverse populations.

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Low vitamin D status is prevalent in many populations and has become a common public health problem worldwide (1,2). Vitamin D is well-known for its essential role in calcium homeostasis and bone health (2). Emerging evidence from both in vitro and in vivo studies has suggested extraskeletal effects of vitamin D, including on insulin action and secretion (2,3). Population studies have provided further support to the hypothesis that low vitamin D status, as assessed by circulating 25-hydroxy vitamin D [25(OH)D] levels, is associated with impaired β-cell function, insulin resistance, and impaired glucose intolerance and thereby may be associated with higher risk of type 2 diabetes (4–7). An inverse association between 25(OH)D levels and prevalent type 2 diabetes has been shown (4,8–10); however, a temporal relationship cannot be established from such cross-sectional studies that are subject to bias due to the possibility of reverse causation. Recently, several prospective observational studies have reported a significant association between high circulating levels of 25(OH)D and lower incidence of type 2 diabetes (11–17). However, no association was observed in other studies (18–21). In addition, individual studies have been underpowered to examine this relation across a broad range of circulating 25(OH)D levels. As highlighted by the recent report on vitamin D from the Institute of Medicine (IOM) (1,22), available evidence on the relation between vitamin D status and type 2 diabetes remains inconsistent and inconclusive, and there is a need for further research to clarify the optimal levels of 25(OH)D for nonskeletal outcomes, including type 2 diabetes, and to assess whether there is a nonlinear relationship between 25(OH)D and diabetes risk. Assessment of possible threshold levels of 25(OH)D will greatly advance our understanding of the magnitude and shape of the association of vitamin D with incidence of type 2 diabetes.

Available evidence from prospective studies with circulating 25(OH)D levels measured in baseline blood samples collected before the onset of disease allow us to address the temporal relation of vitamin D status with risk of type 2 diabetes. We therefore conducted a meta-analysis of prospective studies from various populations to quantify the association between circulating 25(OH)D levels and subsequent risk of type 2 diabetes and examine possible threshold effect of 25(OH)D levels.

RESEARCH DESIGN AND METHODS

Data source and searches

Relevant studies were identified by searching MEDLINE and Embase databases for all published articles up to 31 October

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2012, using the search terms "vitamin D," "25-hydroxy vitamin D," "25(OH)D," "1,25-dihydroxy vitamin D," "1,25(OH)2D," "calcidiol," "calcitriol," "insulin resistance," "insulin secretion," "insulin sensitivity," "glucose intolerance," "glucose metabolism," "beta-cell function," "type 2 diabetes," and "diabetes." The search was further restricted to English-language articles, human studies, and adult subjects aged ≥19 years. Additional studies were retrieved through a hand search of references from original reports. All prospective studies on this topic were considered eligible if they provided data on the relationship between baseline circulating levels of 25(OH)D and risk of type 2 diabetes.

In the first round of screening (n = 542), 470 articles were excluded for at least one of the following reasons: studies that did not study circulating 25(OH)D as an exposure or type 2 diabetes as an outcome (200 articles), studies among children and adolescence populations (4 articles), nonhuman studies (15 articles, including chemistry, animal, cell line, and isolated tissue studies), reviews/editorials/guidelines/letters/commentaries (185 articles), cross-sectional or retrospective studies (61 articles), and case reports (5 articles) (Fig. 1). In the second round of screening, full-text articles were retrieved (n = 72). Sixty-three articles were further excluded for at least one of the following reasons: updated data available from other studies in the same population or duplicate publications (3 articles), diabetes complications as major outcomes (33 articles), association measures for diabetes-related risk factors (19 articles), and lack of directly measured 25(OH)D levels (2 articles using predicted score). Our search strategy and inclusion/exclusion criteria resulted in a total of 21 independent prospective studies (extracting from 15 articles) being included in the current meta-analysis.

Data extraction

Three investigators (Y.S., L.W., and L.C.D.G.) independently reviewed each eligible article and extracted relevant data examining the prospective associations of circulating levels of 25(OH)D with type 2 diabetes risk. Differences, if any, were reconciled through group discussion. Data extracted include population source, study design, follow-up period, sample size, subject characteristics (age, sex, and comorbid conditions), 25(OH)D assay methods, diabetes end points, and main study findings. When results were available only on different subpopulations in the same study (13,14,23), we separately extracted data for each subpopulation (study characteristics described in Supplementary Table 1).

Statistical analysis

To provide quantitative evidence from all studies and maximize statistical power for hypothesis testing, we performed meta-analyses using DerSimonian and Laird's random-effects model with inverse-variance (SE) weighting of individual study results (24) when data could be combined. The summary relative risks (RR) with 95% CI were calculated for the highest versus the lowest category of 25(OH)D levels. We also performed subgroup meta-analyses to explore potential effect modification by prespecified factors, including sex, follow-up duration, sample size of cases, adjustment for BMI, adjustment for BMI and other metabolic parameters (including hypertension, lipids, or inflammatory biomarkers), and 25(OH)D assay methods. Heterogeneity across studies was assessed by Cochran Q statistic. Because the Cochran Q statistic has low statistical power (25), we also calculated the I^2 and H statistics to reflect between-study heterogeneity. The percentage of I^2 ~25 (I^2 = 25), 50 (I^2 = 50), and 75 (I^2 = 75) indicates low, medium, and high heterogeneity, respectively (26). The H statistic is a complement to the I^2 statistic in assessing study heterogeneity; an H <1.2 indicates little heterogeneity, and an H >1.5 raises caution regarding notable heterogeneity (26). We visually assessed publication bias using Begg modified funnel plots, in which the RR was plotted on a logarithmic scale (log[RR]) against its SE from each study. Publication bias was also assessed by two formal tests: Begg adjusted rank correlation test and Egger regression asymmetry test (27,28). The former was used to examine if there was significant correlation between the effect estimates and their variances, and the latter

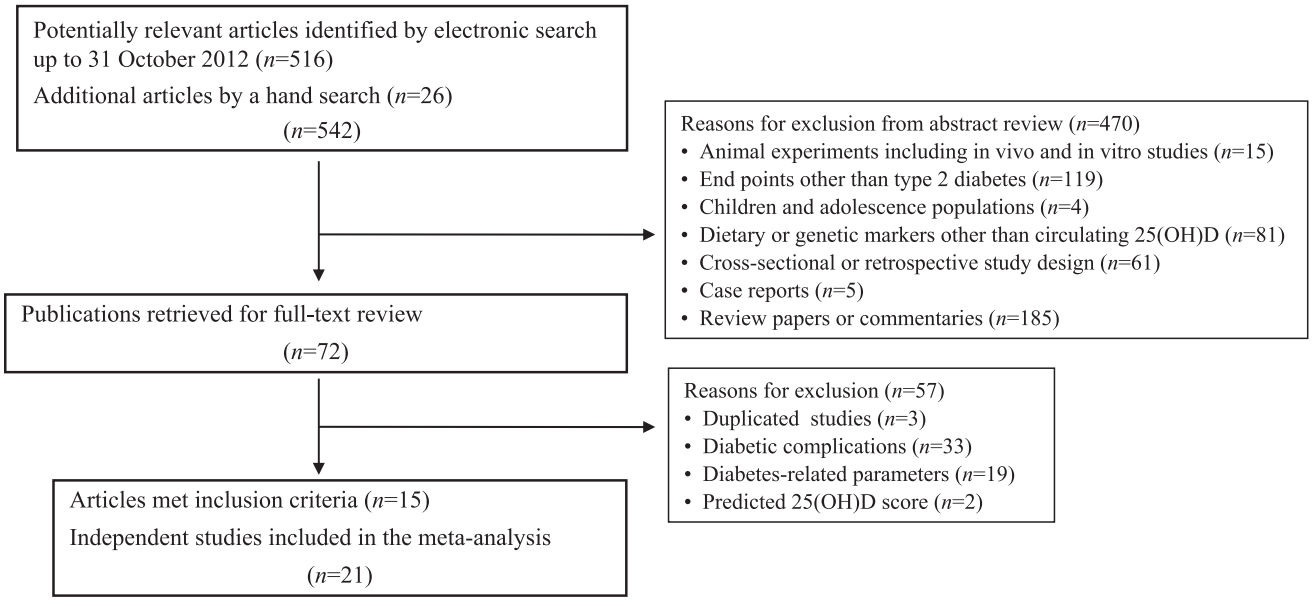

Figure 1—*Flow chart of study selection.*

uses an inverse-variance weighted regression of the effect sizes on their precision (the inverse of SE) to test whether the intercept deviates significantly from zero.

We tested for possible nonlinear association between circulating 25(OH)D levels and type 2 diabetes using a quadratic polynomial spline regression analysis, considering a possibility of data perturbation at an extreme end of the exposure range (29). We also used the method described by Greenland and Longnecker (30) for the dose-response analysis to compute the linear trend from the correlated RRs and 95% CIs across categories of 25(OH)D. The median level of 25(OH)D in each category was assigned to the corresponding RR when reported in the study. If not reported, the values assigned were the means or the midpoint of the lower and upper bound in each category. For extreme open-ended categories, half the width of the adjacent category was subtracted (for the lowest category) or added (for the uppermost category) to obtain the midpoint. The numbers of case and control subjects or person-years by category were also collected if available.

All analyses were performed using the STATA statistical software (Version 10.1; STATA Corp., College Station, TX). Statistical significance was defined as two-tailed $\alpha < 0.05$.

RESULTS—We included 15 publications (11–16,18,19,23,31–33) that met our inclusion criteria in our meta-analysis, which provided data from 21 independent studies [11 cohort studies (11–13,17,18, 20,21,31–33), 8 nested case-control studies (14,15,19,23), and 2 case-cohort studies (16,33)] (Fig. 1). These prospective studies comprised a total of 76,220 participants and 4,996 incident diabetes cases. As summarized in Supplementary Table 1, 13 studies were population-based (12–14,16,17,20,21,23,32,33), and 2 studies included postmenopausal women only (18,19). Nineteen studies included largely whites (11–18,20,21,23,32,33), and 2 studies included multiple racial/ethnic populations (19,31). The outcome of diabetes was ascertained using a combination of criteria, including diabetes-specific pharmacotherapy, diabetes-related hospitalization, self-report, and glycemic status information (11–16,18,19). Five studies used the American Diabetes Association glycemic criteria for diagnosis (20,21,23,31,33). The assay method for 25(OH)D varied across studies. Radioimmunoassay was used in 8 studies (14,15,18,21,33), chemiluminescent immunoassay was used in 10 studies (11–13,16,17,19,23,32), and only 3 studies used liquid chromatography–tandem mass spectrometry, which is the gold standard to measure 25(OH)D (20,31,33).

Hypothesis testing

Fig. 2 shows the summary RR of type 2 diabetes comparing the highest to lowest category of 25(OH)D levels for hypothesis testing. The summary RR was 0.62 (95% CI 0.54–0.70), indicating a significant inverse association between baseline 25(OH)D levels and risk of type 2 diabetes. The *P* value for the Cochran *Q* test was 0.21, the *H* statistic was 1.1 (1.0–1.5), and the I^2 statistic was 19% (0–53), indicating no evidence of significant between-study heterogeneity. The Begg funnel plot for the visual assessment of publication bias showed that smaller RRs with large SEs tended to be above the horizontal line, indicating a possibility of publication bias in favor of small studies with null findings (data not shown). However, the Egger test ($P = 0.39$) and the Begg test ($P = 0.99$) did not show evidence of publication bias.

Sensitivity analysis

We conducted a sensitivity analysis to assess the extent to which individual studies with extremely large RRs influenced the summary RR. The exclusion of the study by Anderson et al. (11) that included the largest sample size and RR estimate reduced between-study heterogeneity but did not appreciably change the summary RR (0.64; 95% CI 0.56–0.73; *P* for *Q* statistic = 0.27, *H* = 1.1 [1.0–1.4], and I^2 = 15% [0–50]). Omitting four studies from the earliest publication by Knekt et al. (14), which included small sample size and heterogeneous results, also did not substantially influence the summary RR (0.61; 95% CI 0.55–0.68; *P* for *Q* statistic = 0.46, *H* = 1.0 [1.0–1.4], and I^2 = 0% [0–51]). The most recent study with the smallest number of cases ($n = 37$) yielded large variance in the effect estimate; removing this study led to almost the same summary RR (0.62; 95% CI 0.56–0.70; *P* for *Q* statistic = 0.35, *H* = 1.0 [1.0–1.3], and I^2 = 9% [0–44]).

Sources of heterogeneity

We evaluated potential effect modifiers in stratified analyses (Table 1). The inverse association between 25(OH)D and diabetes risk was consistently observed in men, women, and a mixed population of men and women. Associations tended to be stronger for men than for women alone, but the difference did not reach statistical significance. Nor did duration of follow-up, study sample size, diabetes diagnostic criteria, and 25(OH)D assay methods influence the summary RRs. Several studies presented RRs for 25(OH)D levels and type 2 diabetes with and without adjustment for metabolic variables, including BMI, hypertension, markers of glycemia and insulin sensitivity, plasma lipid levels, or inflammatory markers. The associations between 25(OH)D levels and diabetes risk were attenuated but remained statistically significant after adjustment for BMI and hypertension and/or other biomarkers: the RRs were 0.52 (95% CI 0.46–0.58) and 0.63 (0.56–0.72) in the models without and with adjustment for these covariates, respectively (*P* for interaction = 0.02). Likewise, adjustment for BMI alone slightly attenuated the association (*P* for interaction = 0.06).

Dose-response analysis

Fig. 3 shows the dose-response relation between circulating 25(OH)D and risk of type 2 diabetes. Overall, the test for a linear relation across the range of 25(OH)D from 20 up to 160 nmol/L was significant ($P < 0.0001$). The RR for type 2 diabetes was 0.96 (95% CI 0.94–0.97) per 10 nmol/L increment in 25(OH)D. A significantly lower risk of type 2 diabetes became evident when 25(OH)D approximated 50 nmol/L. Because most studies had 25(OH)D ranges <100 nmol/L, current evidence for the relation of 25(OH)D of >100 nmol/L with type 2 diabetes was weak.

CONCLUSIONS—On the basis of 21 prospective studies including 4,996 incident cases of type 2 diabetes and 76,220 nondiabetic controls, our meta-analysis showed a significantly inverse association between 25(OH)D levels and incidence of type 2 diabetes. The association was consistent and did not differ appreciably by sex, study size, follow-up duration, diabetes diagnosis criteria, or 25(OH)D assay methods. The association was attenuated but remained significant after adjustment for BMI and/or intermediate biomarkers.

Blood 25(OH)D levels, which reflect all sources of vitamin D exposure and have a half-life of 2 to 3 weeks, have been widely used as a surrogate of vitamin D status (2,3). Due to differences in assay

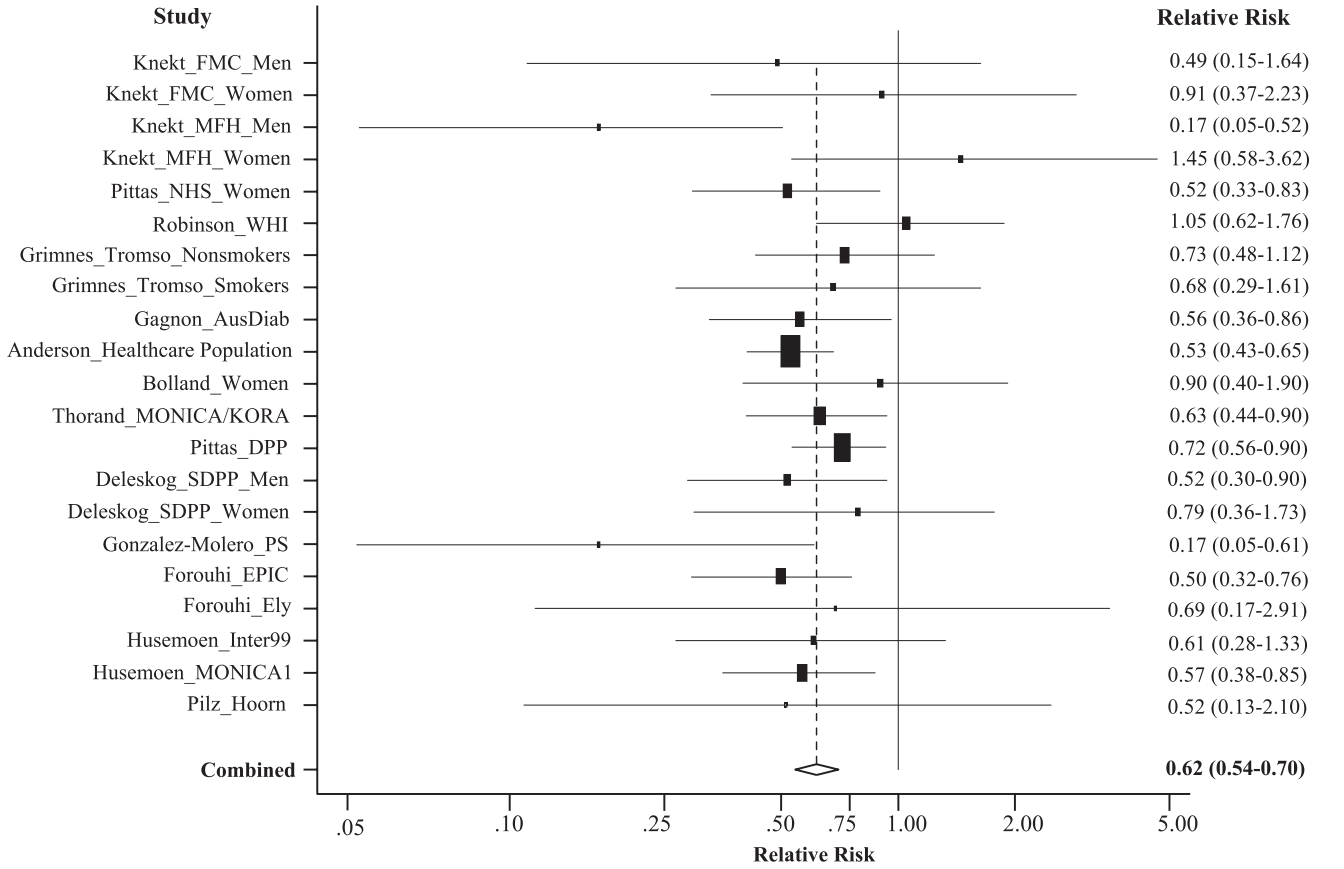

Figure 2—*A random-effects meta-analysis of 21 independent prospective studies with adjusted RR and 95% CI of type 2 diabetes in relation to serum 25(OH)D levels (the highest category versus the lowest category). AusDiab, Australian Diabetes, Obesity and Lifestyle Study; DPP, Diabetes Prevention Program; Ely, Medical Research Council Ely Study; EPIC, European Prospective Investigation into Cancer-Norfolk Study; FMC, Finnish Mobile Clinic Health Examination Survey; Hoorn, Hoorn Study; Inter99, Inter99 Study; MFH, Mini-Finland Health Survey; MONICA1, Danish MONICA1 survey; MONICA/KORA, Monitoring of Trends and Determinants in Cardiovascular Disease/Cooperative Health Research in the Region of Augsburg Study; NHS, Nurses' Health Study; PS, Pizarra Study; SDPP, Stockholm Diabetes Prevention Program.*

methods and population characteristics, there is no consensus on the cutoff values defining vitamin D insufficiency or deficiency. Vitamin D insufficiency has been previously reported to range from levels of 40–75 nmol/L (16–30 ng/mL), and vitamin D deficiency is generally defined as levels of <50 nmol/L (20 ng/mL) (2,34). Using 25(OH)D levels ≤50 nmol/L (20 ng/mL) to define vitamin D deficiency, data from 4,495 adults in the National Health and Nutrition Examination Survey 2005–2006 showed that the overall prevalence of vitamin D deficiency was 41.6%, with the highest rate found in blacks (82.1%), followed by Hispanics (62.9%), others (57.6%), and whites (30.9%) (35). The IOM's new guidelines for vitamin D intake and desirable blood levels, which were based on a systematic scientific review of available evidence at the time (1,22), state that a level of 50 nmol/L (20 ng/mL) of serum 25(OH)D is needed to maintain bone health for most individuals. The IOM report called for additional research to clarify the relation of vitamin D levels with nonskeletal outcomes (1,22).

The optimal 25(OH)D levels for type 2 diabetes prevention remain unknown. Epidemiological evidence relating lower circulating vitamin D levels to hyperglycemia, insulin resistance, or type 2 diabetes primarily derives from cross-sectional reports (4,8–10). Prospective data are limited and have been inconclusive (36). Our dose-response curve showed an inverse and significant relation between 25(OH)D and type 2 diabetes across a broad range of 25(OH)D levels in diverse populations. Our results also confirmed that baseline 25(OH)D levels ≥50 nmol/L were significantly associated with a lower risk of type 2 diabetes, although further studies with higher power are required to provide more stable estimates of this association.

The observed inverse association did not differ by sex, study sample size, duration of follow-up, diabetes diagnosis criteria, and 25(OH)D assay methods. An early pooled analysis of 2 nested case-control studies of 412 incident cases of type 2 diabetes and 986 control subjects found a strong inverse association in men but not in women (14). However, this finding of sex-specific relation of 25(OH)D with type 2 diabetes was not confirmed by subsequently published studies nor by our meta-analysis. It is likely that such sex difference resulted from residual confounding or statistical fluctuation due to small sample size. Adiposity is another important covariate in vitamin D–diabetes relation. The interrelationship between vitamin D status and adiposity is complex and possibly bidirectional. Increased storage of 25(OH)D in adipose tissue and less sun exposure due to limited mobility and/or excessive subcutaneous fat deposits in obese individuals will lead to low circulating levels of 25(OH)D (2,3). Conversely, vitamin D may directly affect adiposity

Table 1—*Subgroup analyses for the relation between circulating 25(OH)D and type 2 diabetes*

	No. of studies	Summary RR (95% CI)	*P* value for heterogeneity			*P* value for interaction
			Q test	*H* (95% CI)	I^2 (95% CI)	
All studies	21	0.62 (0.54–0.70)	0.21	1.1 (1.0–1.5)	19 (0–53)	
Sex						0.13
Men	4	0.52 (0.30–0.90)	0.07	1.6 (1.0–2.7)	59 (0–86)	
Women	7	0.76 (0.61–0.95)	0.34	1.1 (1.0–2.0)	12 (0–74)	
Men and women	14	0.60 (0.53–0.66)	0.74	1.0 (1.0–1.5)	0 (0–55)	
Duration of follow-up						0.78
<10 years	9	0.63 (0.51–0.77)	0.11	1.3 (1.0–1.9)	39 (0–72)	
≥10 years	11	0.60 (0.50–0.73)	0.35	1.1 (1.0–1.4)	10 (0–49)	
Sample size of cases						0.59
<200	10	0.65 (0.51–0.83)	0.31	1.1 (1.0–1.5)	14 (0–56)	
≥200	10	0.60 (0.51–0.71)	0.15	1.2 (1.0–1.8)	32 (0–68)	
Adjustment for BMI						0.06
No	6	0.54 (0.47–0.61)	0.72	1.0 (1.0–1.8)	0 (0–68)	
Yes	6	0.66 (0.56–0.77)	0.64	1.0 (1.0–2.0)	0 (0–75)	
Adjustment for BMI or hypertension						0.02
No	12	0.52 (0.46–0.58)	0.42	1.0 (1.0–1.6)	3 (0–60)	
Yes	12	0.63 (0.56–0.72)	0.50	1.0 (1.0–1.5)	0 (0–57)	
Assay method for 25(OH)D						0.81
Radioimmunoassay	8	0.64 (0.43–0.95)	0.17	1.2 (1.0–1.8)	32 (0–70)	
Chemiluminescence immunoassay	9	0.60 (0.51–0.71)	0.21	1.2 (1.0–1.7)	26 (0–65)	
Diagnostic tools for type 2 diabetes						0.49
OGTT	7	0.65 (0.53–0.80)	0.41	1.0 (1.0–1.9)	2 (0–71)	
Self-report	4	0.71 (0.52–0.96)	0.20	1.2 (1.0–2.1)	35 (0–77)	
Others	10	0.58 (0.48–0.70)	0.24	1.1 (1.0–1.6)	22 (0–62)	

OGTT, oral glucose tolerance test.

and other metabolic parameters such as dyslipidemia, hypertension, and systemic inflammation that mediate the pathway from vitamin D status to type 2 diabetes (36,37). In this sense, adiposity could be considered as a confounder or an intermediate variable. Adjustment for adiposity and other obesity-related metabolic parameters may be an overadjustment, possibly underestimating the true association. Finally, with the exception of one study (31), all studies used a single measurement of 25(OH)D at baseline, which is not a time-integrated measure of vitamin D status. 25(OH)D was also assayed using different methods in previous studies. There was substantial intra- and interassay variation in 25(OH)D levels (38). However, the summary RR of type 2 diabetes in relation to 25(OH)D did not differ by assay methods.

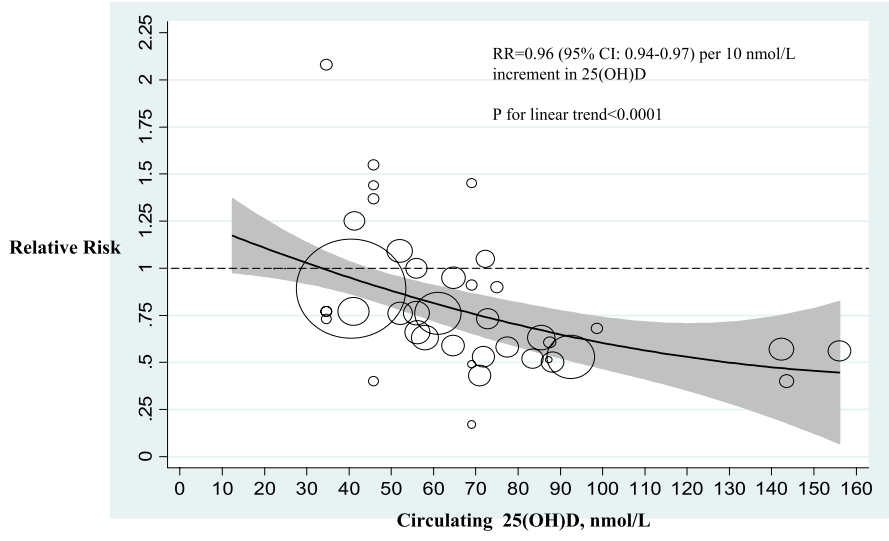

Figure 3—*Relation between the risk of type 2 diabetes and baseline levels of 25(OH)D in 18 independent prospective studies included in the meta-analysis. The relation is modeled by the quadratic spline regression. Circles indicate RR in each study. The circle size is proportional to the precision of the RR (inverse of variance). The gray-shaded region shows the 95% CIs around the regression line.*

Our findings of an inverse relation between 25(OH)D and type 2 diabetes are supported by biological evidence that vitamin D may be implicated in the pathogenesis of diabetes and its complications (36,37). A large body of literature has suggested that optimal vitamin D homeostasis is essential for insulin action and secretion (2,3), two fundamental features in the pathogenesis of type 2 diabetes. Clearly, direct evidence from ongoing (39) and future clinical trials of higher-dose vitamin D supplementation is warranted to clarify any beneficial effects of vitamin D on primary prevention of type 2 diabetes.

Findings from our meta-analysis of observational studies will augment and complement findings from randomized trials of the effect of vitamin D supplements on type 2 diabetes. Although randomized trials are critical for establishing cause-and-effect relationships between vitamin D supplementation and health outcomes, they will not address all the potential questions because of their fixed dose (or at most, a few doses) of vitamin D and narrow range of 25(OH)D levels achieved by supplementation. Prospective observational studies allow us to assess 25(OH)D thresholds for diabetes risk across a broad spectrum of 25(OH)D levels. The largest randomized trial of vitamin D supplement to date, the Women's Health Initiative (WHI) Clinical Trial, has evaluated vitamin D plus calcium supplementation for fracture prevention in >36,000 postmenopausal women (40). Secondary analysis of the WHI trial with 33,951 initially nondiabetic women did not observe any effect from daily intake of 1,000 mg elemental calcium plus 400 IU vitamin D3 on incident diabetes over 7 years of follow-up (40). Of note, a dose of 400 IU/day vitamin D in the WHI raised median levels of serum 25(OH)D from 42.3 to only 54.1 nmol/L (~12 nmol/L), which is below the optimal value of 75 nmol/L or more for skeletal and nonskeletal health including type 2 diabetes (41). Similarly, secondary analysis of another large randomized trial, the Randomized Evaluation of Calcium Or vitamin D (RECORD) trial, did not observe any effect from daily intake of 800 IU vitamin D3 on incident diabetes over 2–5 years, although such a daily dose raised serum 25(OH)D from 38 to 62 nmol/L on average (42).

Our meta-analysis has some limitations. First, the observational nature of prospective studies included in our analysis cannot rule out residual confounding, although the consistency of our results across multiple strata and sensitivity analyses minimizes the likelihood that residual confounding explains the findings. Second, as in any meta-analysis, publication bias is possible, although our visual examination and formal tests did not suggest the presence of substantial publication bias. Finally, limited data from existing prospective studies lacked sufficient power to detect potential sex- or ethnicity-specific 25(OH)D thresholds or dose-response relations.

In conclusion, our meta-analysis of 21 prospective studies demonstrates a significant inverse association between circulating 25(OH)D levels and risk of incident type 2 diabetes in a dose-response manner across a wide spectrum of 25(OH)D levels. Direct evidence from future randomized trials is warranted to clarify a cause-and-effect relationship between vitamin D and type 2 diabetes.

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No potential conflicts of interest relevant to this article were reported.

Y.S. did the literature search and data extraction, selected the studies, carried out the statistical analyses, wrote the first draft of the original manuscript, and contributed to discussion. L.W. did the literature search and data extraction, selected the studies, and contributed to discussion. A.G.P., C.Z., J.E.M., and F.B.H. contributed to discussion. L.C.D.G. did the literature search and data extraction, selected the studies, and contributed to discussion.

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